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(54) Title: A MEMBRANE OR MATRIX FOR CONTROLLING THE PERMEATION RATE OF DRUGS

(57) Abstract

The invention relates to a membrane or matrix for controlling the permeation rate of a drug, wherein said membrane or matrix comprises a siloxane–based elastomer composition which comprises at least one elastomer and possibly a non–crosslinked polymer. The elastomer composition comprises poly(alkylene oxide) groups, and the poly(alkylene oxide) groups are present in the elastomer or the polymer as alkoxy–terminated grafts of polysiloxane units, or as blocks, the said grafts or blocks being linked to the polysiloxane units by silicon–carbon bonds, or as a mixture of these forms. The invention also relates to methods for the preparation of the elastomer composition to be used in said membrane or matrix.

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A MEMBRANE OR MATRIX FOR CONTROLLING THE PERMEATION RATE OF DRUGS

The invention relates to a membrane or matrix intended for controlling the permeation rate of a drug, wherein said membrane or matrix comprises a siloxane-based elastomer composition, and to a method for the preparation of said elastomer composition.

STATE OF THE ART

Polysiloxanes, in particular poly(dimethyl siloxane) (PDMS), are highly suitable for use as a membrane or matrix regulating the permeation rate of drugs in various drug forms, in particular in implants and IU systems. Polysiloxanes are physiologically inert, and a wide group of drugs are capable of penetrating polysiloxane membranes, which also have the required strength properties.

It is known from the literature that the adding of poly-(ethylene oxide) groups, i.e. PEO groups, to a PDMS polymer may increase the permeation rate of drugs. Publication KL Ullman et al., Journal of Controlled Release 10 (1989) 251-260, describes membranes prepared from a block copolymer which contains PEO and PDMS and the penetration of various steroids through these membranes. It is noted in the publication that an increasing PEO amount in the block polymer tends to increase the penetration of hydrophilic steroids, while the penetration of lipophilic steroids decreases. The block copolymer described in the publication is very complicated in its structure and preparation, and would therefore not be facile in more extensive technical production.

OBJECT OF THE INVENTION

The object of the invention is to provide an elastomer composition which is easy to prepare, through which a drug

migrates at the desired rate, and which gives the membrane the required mechanical properties.

The object of the invention is in particular to provide an elastomer composition through which the permeation rate of drugs with hormonal action can be controlled.

SUMMARY OF THE INVENTION

The invention thus relates to a membrane or matrix intended for controlling the permeation rate of a drug, said membrane or matrix comprising a siloxane-based elastomer composition comprising at least one elastomer and possibly a non-crosslinked polymer. The invention is characterized in that the elastomer composition comprises poly(alkylene oxide) groups and that the poly(alkylene oxide) groups are present in the elastomer or polymer as alkoxy-terminated grafts of polysiloxane units, or as blocks, the said blocks or grafts being linked to the polysiloxane units by silicon-carbon bonds, or as a mixture of these forms.

The invention also relates to a method for the preparation of a siloxane-based elastomer which comprises poly(alkylene oxide) groups and is intended for use in a membrane or matrix for controlling the permeation rate of drugs. The method is characterized in that a) a vinyl-functional polymer component and a hydride-functional component are crosslinked in the presence of a catalyst, or that b) a polymer component is crosslinked in the presence of a peroxide catalyst.

DETAILED DESCRIPTION OF THE INVENTION

General description of the elastomer composition

The term "elastomer composition" may stand for one single elastomer, in which case the polysiloxane units which contain poly(alkylene oxide) groups are present in the said

elastomer.

According to another embodiment, the elastomer composition may be made up of two elastomers which are interlaced, one inside the other. In this case the first elastomer comprises poly(alkylene oxide) groups so that the poly(alkylene oxide) groups are present in the said elastomer either as alkoxy-terminated grafts of polysiloxane units or as blocks, the said grafts or blocks being linked to the polysiloxane units by silicon-carbon bonds. The poly(alkylene oxides) may also be present as a blend of the options mentioned. The second elastomer may be a siloxane-based elastomer, suitably a poly(dimethyl siloxane)-based elastomer. The said second elastomer may possibly also comprise poly(alkylene oxide) groups. These poly(alkylene oxide) groups may also be present either as alkoxy-terminated grafts of poly(dimethyl siloxane) units or as blocks, the said grafts or blocks being linked to the poly(dimethyl siloxane) units by silicon-carbon bonds. The poly(alkylene oxides) may also in this elastomer be present as a blend of the options mentioned above.

According to a third embodiment, the elastomer composition may be a blend which comprises a siloxane-based elastomer, which is, for example, made up of PDMS, and at least one straight-chain polysiloxane copolymer which comprises poly(alkylene oxide) groups. In this case the poly(alkylene oxide) groups are present in the said polymer either as alkoxy-terminated grafts of polysiloxane units or as blocks, the said grafts or blocks being linked to the polysiloxane units by silicon-carbon bonds. The poly(alkylene oxide) groups may, of course, also be present in the polymer as a blend of the forms mentioned. In this embodiment, also the siloxane-based elastomer may comprise poly(alkylene oxide) groups, in which case these poly(alkylene oxide) groups are present in the elastomer either as alkoxy-terminated grafts of polysiloxane units or as blocks, the said blocks or grafts being linked to the

polysiloxane units by silicon-carbon bonds. The poly(alkylene oxide) groups may also be present as a blend of the forms mentioned.

Of course, the elastomer composition may also be made up of two elastomers interlaced one inside the other, as above, and at least one straight-chain polysiloxane copolymer which comprises poly(alkylene oxide) groups.

The poly(alkylene oxide) groups of the elastomer composition may suitably be, for example, poly(ethylene oxide) groups (PEO groups).

The polysiloxane units of the elastomer composition are preferably groups having the formula

$$-(SiR'R''O)_qSiR'R''-$$

where R' and R'' are
- partly free groups, which are the same or different and which are a lower alkyl group, or a phenyl group, in which case the said alkyl or phenyl groups may be substituted or unsubstituted, or alkoxy-terminated poly(alkylene oxide) groups having the formula

$$-R^3-O-(\underset{\displaystyle R}{\underset{|}{CH}}-CH_2-O)_m-alk,$$

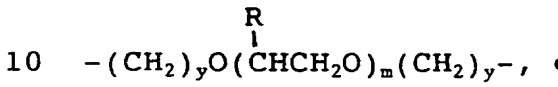
where alk is a lower alkyl group, suitably methyl, R is hydrogen or a lower alkyl, m is 1...30, and R^3 is a straight or branched C_2 - C_6 alkyl group,
- partly bonds, formed from the hydrogen or alkylene groups, to other polymer chains in the elastomer, and
- possibly partly unreacted groups, such as hydrogen, vinyl or vinyl-terminated alkene, and
- q is 1...3000.

The term "lower alkyl" stands here and generally in the description of the present invention for C_1 - C_6 alkyl groups.

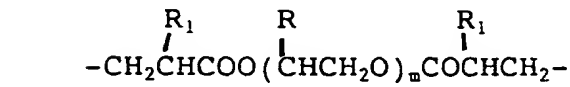
The above-mentioned free R' and R'' groups are suitably a lower alkyl group, preferably methyl.

The term "poly(alkylene oxide) group" means that said group comprises at least two alkyl ether groups successively connected to each other.

According to a preferred embodiment, the poly(alkylene oxide) groups are present in the elastomer in the form of poly(alkylene oxide) blocks having the formula



$$-(CH_2)_yO(\underset{R}{CHCH_2O})_m(CH_2)_y-, \text{ or}$$



$$-CH_2\underset{R_1}{CH}COO(\underset{R}{CHCH_2O})_mCO\underset{R_1}{CH}CH_2-$$

where R is hydrogen, a lower alkyl or a phenyl, R_1 is hydrogen or a lower alkyl, y is 2...6, and m is 1...30.

The elastomer composition suitably contains a filler, such as silica, in order that the membrane should obtain a sufficient strength.

The word "membrane" means the same as film.

General description of the method for the preparation of the elastomer composition

According to a preferred embodiment, the novel elastomer is prepared by crosslinking, in the presence of a catalyst, a vinyl-functional polymer component and a hydride-functional siloxane component.

By crosslinking is meant the addition reaction of the hydride-functional siloxane component with the carbon-carbon double bond of the vinyl-functional polymer

component.

According to another embodiment, the elastomer is prepared by crosslinking the polymer in the presence of a peroxide catalyst. In this case the vinyl and methyl groups react with each other and form carbon-carbon bonds. A crosslink may also be formed between two methyl groups or between two vinyl groups.

For crosslinking, the amounts of the components are preferably selected so that the ratio of the molar amounts of the hydrides and the double bonds is at least 1.

The vinyl-functional polymer component may be

a) a vinyl-functional polysiloxane having the formula

$R'-SiR'R''O(SiR'R''O)_rSiR'R''R'$

where R' and R'' are the same or different, and are a lower alkyl group, or a phenyl group, in which case the said alkyl or phenyl group may be substituted or unsubstituted, and where some of the substituents R' and/or R'' have been substituted for by vinyl groups, and r is 1...27000, or

b) an alkenyl terminated polysiloxane-based block copolymer having the formula

$T(AB)_xAT$ (I), where

$A = -(SiR'R''O)_qSiR'R''-$, where R' and R'' are the same or different and are a lower alkyl group, or a phenyl, in which case the said alkyl or phenyl group may be substituted or unsubstituted;

B is a poly(alkylene oxide) having the formula

$$-R^3O(\overset{R}{\overset{|}{C}}HCH_2O)_mR^4-, \text{ or}$$

$$-CH_2\overset{R_1}{\overset{|}{C}}HCOO(\overset{R}{\overset{|}{C}}HCH_2O)_mCO\overset{R_1}{\overset{|}{C}}HCH_2-,$$

and T is

$$R^1O(\overset{R}{\overset{|}{C}}HCH_2O)_mR^{3-}, \text{ or}$$

$$CH_2{=}\overset{R_1}{\overset{|}{C}}COO(\overset{R}{\overset{|}{C}}HCH_2O)_mCO\overset{R_1}{\overset{|}{C}}HCH_2-$$

where
R is hydrogen, a lower alkyl or phenyl, R_1 is hydrogen or a lower alkyl, R^3 and R^4 are the same or different and are straight-chain or branched C_2 - C_6 alkylene groups, R^1 is a straight-chain or branched C_2 - C_6 alkenyl group, m is 1...30, q is 1...3000, and x is 0...100, or

c) a vinyl-functional polysiloxane copolymer having the formula

$$R'-SiR'R''O(SiR'R''O)_r(SiR'R''O)_pSiR'R''-R'$$

- where in the first block R' and R'' are the same or different and are a lower alkyl group, or a phenyl group, in which case the said alkyl or phenyl group may be substituted or unsubstituted, and where some of the substituents R' and/or R'' have been substituted for by vinyl groups, and r is 1...27000, and

- where in the second block R' is a lower alkyl group, or an alkoxy-terminated poly(alkylene oxide) group having the formula

$-R^3-O-(\overset{R}{\overset{|}{C}}H-CH_2-O)_m$-alk, where alk is a lower alkyl group, suitably methyl, R is hydrogen or a lower alkyl group, R^3 is a straight or branched C_2 - C_6 alkyl, and m is 1...30, or R' is a phenyl group, in which case the said alkyl or phenyl group may be substituted or unsubstituted, and R'' is a lower alkyl or a phenyl group, in which case the said alkyl or phenyl group may be substituted or unsubstituted, and p is 1...5000, or

d) α,ω-dialkenyl poly(alkylene oxide) having the formula

$$R^1-O-(\overset{R}{\overset{|}{C}}H_2CH_2O)_m-R^2$$

where R^1 and R^2 are the same or different straight-chain or branched C_2 - C_6 alkenyl groups, R is hydrogen or a lower alkyl, and m is 1...30, or

e) a blend of at least two of the above-mentioned components a) - d).

If the formula of the vinyl-functional polysiloxane copolymer is, in accordance with the above description, $R'-SiR'R''O(SiR'R''O)_r(SiR'R''O)_pSiR'R''-R'$, it should be noted that the formula is a kind of gross formula, in which the blocks in successive parentheses may appear in any order in relation to one another. Furthermore, it is preferable that both a vinyl group and the above-mentioned alkoxy-terminated poly(alkylene oxide) group are not bonded to one and the same Si atom.

The hydride-functional component may be

a) a hydride-functional siloxane, which may be straight-chain, star shaped, branched or cyclic, or

b) a hydride-terminated siloxane-based block copolymer

having the formula

$T(BA)_xBT$ (II), where

T = $H\text{-}SiR'R''O(SiR'R''O)_qSiR'R''\text{-}$,

A = $\text{-}SiR'R''O(SiR'R''O)_qSiR'R''\text{-}$, where R' and R'' are the same or different and are a lower alkyl group or a phenyl group, in which case the said alkyl or phenyl group may be substituted or unsubstituted;

B is a poly(alkylene oxide) having the formula

$\text{-}R^3\text{-}O(\overset{R}{\overset{|}{C}}HCH_2O)_mR^4\text{-}$, or

$$\text{-}CH_2\overset{R_1}{\overset{|}{C}}HCOO(\overset{R}{\overset{|}{C}}HCH_2O)_m\text{CO}\overset{R_1}{\overset{|}{C}}HCH_2\text{-}$$

where R is hydrogen, a lower alkyl or a phenyl, R_1 is hydrogen or a lower alkyl, R^3 and R^4 are the same or different and are straight-chain or branched C_2 - C_6 alkyl groups, m is 1...30, q is 1...3000, and x is 0...100, or

c) a blend of the above-mentioned components a) and b).

According to one embodiment, the hydride-functional siloxane copolymer may be straight-chain, in which case its formula is

$R'\text{-}SiR'R''O(SiR'R''O)_rSiR'R''R'$

where R' and R'' are the same or different and are a lower alkyl group, or a phenyl group, in which case the said alkyl or phenyl group may be substituted or unsubstituted, and where some of the substituents R' and/or R'' have been substituted for by hydrogen, and r is 1...27000.

The vinyl-functional polymer component may contain a filler, suitably silica.

The catalyst to be used in the crosslinking is suitably a noble metal catalyst, most commonly a platinum complex in alcohol, xylene, divinyl siloxane or cyclic vinyl siloxane. An especially suitable catalyst is a Pt(0)-divinyl-tetramethyl disiloxane complex.

The elastomer composition made up of two elastomers is prepared so that initially a first elastomer is formed, whereafter a second elastomer is formed by crosslinking in the presence of the first elastomer. Thus the second elastomer will penetrate through the first elastomer.

The elastomer composition which comprises an elastomer and a straight-chain polymer is prepared, for example, by blending a vinyl-functional polymer component, a hydride-functional component, and a polymer which has no vinyl or hydride groups. In the crosslinking, the vinyl-functional polymer component and the hydride-functional component form an elastomer, but the polymer component which does not contain the said functional groups will not take part in the crosslinking reaction but will remain, in a straight-chain form, inside the elastomer.

EXPERIMENTAL SECTION

The invention is described below in greater detail with the help of examples.

Elastomer compositions of different types (A - J) were prepared. Of most composition types there were prepared different compositions which differed one from another with respect to the PEO amount. Elastomer membranes representing the different compositions were tested with respect to the permeation rates of various drugs.

Elastomer compositions prepared

In the elastomer compositions A - H described below, an addition reaction between vinyl groups and silyl hydride groups was used for the crosslinking, i.e. for producing a network structure. The hydride-functional siloxane polymer serving as the crosslinking agent contained at least two Si-H groups, which reacted with the carbon-carbon double bond of the polymer to be crosslinked. Membranes made from elastomer compositions I and J were prepared by using peroxide as the catalyst for crosslinking, in which case the vinyl or methyl groups reacted, forming carbon-carbon bonds. In all the composition types except composition types A, D, F and H, there was first prepared a basic polymer blend, in which case all of the vinyl-containing polymers and the fillers, or vinyl-containing polymers which contained a filler, were mixed together. The filler used was silica. Composition types A, D, F and H had only one vinyl-containing polymer each, and thus they themselves were basic polymers. The basic polymer blend was divided into portions I and II. The catalyst was added to portion I and the crosslinking agent and the inhibitor to portion II. Portions I and II were combined immediately before the crosslinking. The obtained blend was crosslinked at a temperature which was higher than the decomposition temperature of the inhibitor and at which the crosslinking reaction took place at the desired velocity.

A blend can be made of the compositions also directly in one step, in which case the ingredients can be added in the following order: vinyl-containing polymers, inhibitor, catalyst and crosslinking agent.

The following table describes elastomer membranes of different composition types and their initial components.

Table 1

Composition type	Polymers containing vinyl groups in the basic polymer blend	Crosslinking agent
A	α,ω-divinyl ether poly(ethylene oxide)-poly(dimethyl siloxane) multi-block copolymer (PEO-(-PDMS-PEO)$_n$)	Hydride-functional siloxane
B	PEO-(PDMS-PEO)$_n$ and a siloxane polymer containing a filler	Hydride-functional siloxane
C	PEO-(PDMS-PEO)$_n$ together or separately with a siloxane polymer which does or does not contain a filler	α,ω-bis(dimethyl silyl hydride)-poly(dimethyl siloxane)-poly(ethylene oxide) multi-block copolymer (PDMS-(PEO-PDMS)$_n$) together or separately with a hydride-functional siloxane.
D	α,ω-divinyl ether poly(ethylene oxide (PEODIVI)	Hydride-functional siloxane
E	PEODIVI and a siloxane polymer which does or does not contain a filler	Hydride-functional siloxane
F	PEO-grafted dimethyl siloxane-methyl vinyl siloxane copolymer (PDMS-PEO graft copolymer)	Hydride-functional siloxane
G	PDMS-PEO graft copolymer and a siloxane polymer which does or does not contain a filler	Hydride-functional siloxane
H	α,ω-diallyl ether poly(ethylene oxide)-poly(dimethyl siloxane) multi-block copolymer (APEO-(-PDMS-APEO)$_n$)	Hydride-functional siloxane
I	PEO-(PDMS-PEO)$_n$ and a siloxane polymer which does or does not contain a filler	Peroxide
J	PDMS-PEO graft copolymer together or separately with a siloxane polymer which does or does not contain a filler	Peroxide

EXAMPLE 1

Elastomer membrane prepared from composition type A

Ingredients used for the preparation of the elastomer membrane:

- α,ω-divinyl ether PEO-PDMS block copolymer where the amount of PEO was 27.0 % by weight and the vinyl content was 0.186 mmol/g.

- Platinum catalyst Silopren U Katalysatoren Pt-D (Bayer AG), which had a platinum-siloxane complex in a vinyl-containing siloxane matrix. The platinum content was 1 % by weight and the vinyl content was 0.5 mmol/g.

- Crosslinking agent α,ω-di(trimethyl silyl) dimethyl siloxane-hydromethyl siloxane (DMS-HMS) copolymer Silopren U Vernetzer 730 (Bayer AG) having a Si-H content of 7.1 mmol/g, a molar mass of 2800 g/mol and a DMS group to HMS group ratio of 1:1.

- Inhibitor 1-ethinyl-1-cyclohexanol (ETCH, Aldrich) having a decomposition temperature of +40 °C.

The $PEO(-PDMS-PEO)_n$ which was used as the initial substance was prepared as follows:

50 g of anhydrous α,ω-divinyl ether poly(ethylene oxide) (PEODIVI) having a molar mass of 268 g/mol was weighed into a three-necked flask. In addition, 129.87 g of α,ω-bis(dimethyl silyl hydride) poly(dimethyl siloxane) (PDMSDIH, M_n = 717 g/mol) and 30 % by weight of toluene dried by distillation were weighed into the same vessel. Since vinyl groups were present in excess (3 %) in the reaction, in the final product vinyl groups were obtained at both ends, which was essential for the subsequent crosslinking. The reaction solution was stirred over a

magnetic stirring plate at 200 rpm, and dry oxygen was directed through the solution in order to prevent the deactivation of the catalyst. The reaction solution was heated to 50 °C, whereafter the catalyst (Pt(0) divinyltetramethyl disiloxane complex) was added to the solution through the septum. The amount of platinum was 30 ppm, calculated from the amount of reactants. Thereafter the polymerization was monitored by means of IR until the reactions were complete (loss of the Si-H peak at 2130 cm^1), which took approximately 4 h. After the polymerization, the toluene was distilled off from the solution by raising the temperature to 65 °C and by lowering the pressure to 5 mbar for a period of 1 h.

In the preparation of the elastomer, two blends were first prepared, portions I and II. Portion I contained PEO-(PDMS-PEO)$_n$ and the platinum catalyst. Portion II contained PEO-(PDMS-PEO)$_n$, the crosslinking agent and the inhibitor. Portions I and II were combined by mixing immediately before the crosslinking.

The amounts of the ingredients in the composition example in the final blend to be crosslinked were as follows:

- Basic polymer PEO-(PDMS-PEO)$_n$ 94.87 % by weight
- Platinum catalyst 0.1 % by weight
- Crosslinking agent 5.00 % by weight
- Inhibitor 0.03 % by weight

Portion I was prepared using a chamber mixer. 5.489 g of the basic polymer and 0.011 g of the platinum catalyst were weighed into the mixing chamber. The ingredients were agitated until the blend was homogeneous.

The crosslinking agent and the inhibitor were combined before being mixed with portion II. The mixture of the crosslinking agent and the inhibitor was prepared by weighing 0.059 g of ETCH and 9.941 g of Silopren U

Vernetzer 730 into a glass vessel and by stirring the mixture in a water bath of +37 °C until ETCH had dissolved completely in the crosslinking agent. The amount of inhibitor in the mixture was 0.59 % by weight.

Portion II was prepared using a chamber mixer. The mantle of the chamber mixer was cooled by water circulation to a point below room temperature, whereupon the temperature increase due to friction did not raise the temperature to the decomposition temperature of the inhibitor. 4.947 g of PEO-PDMS block copolymer and 0.553 g of the mixture of the crosslinking agent and the inhibitor were weighed into the mixing chamber. The ingredients were agitated until the blend was homogeneous.

Portions I and II were combined immediately before the crosslinking, by adding 5 grams of portion I and 5 grams of portion II into the mixing chamber of the chamber mixer. The ingredients were agitated until the blend was homogeneous. The blend was recovered and was drawn into vacuum to remove air bubbles. Four batches of 2 g of the blend were weighed and crosslinked successively in a hot-press.

The weighed blend was placed between two FEP release membranes in the center of a round metal form having a thickness of 0.4 mm and an inner diameter of 8 cm. The blend, together with the forms and the FEP membranes, was placed between the compression surfaces of the hot-press, which surfaces had been heated in advance to +115 °C. The surfaces were pressed together and were kept pressed at a pressure of 200 bar for 5 minutes. The pressure was released and the membrane was allowed to set at room temperature for 24 hours. Round test pieces having a diameter of 22 mm were cut out from the membranes by means of a puncher.

EXAMPLE 2

Elastomer membrane prepared from composition type B

Ingredients used for the preparation of the elastomer membrane:

- The PEO(-PDMS-PEO)$_n$ was the same as in Example 1, except that the amount of PEO had been increased to 28.0 % by weight and the vinyl content to 0.24 mmol/g by increasing the proportion of PEODIVI in the synthesis of the block copolymer.

- The catalyst, the crosslinking agent and the inhibitor were the same as in Example 1.

The siloxane polymer which contained filler was a dimethyl siloxane-vinyl methyl siloxane (DMS-VMS) copolymer containing a silica filler and having a molar mass of M_n = 400,000 g/mol. The vinyl content of the blend was 0.011 mmol/g. There was 36 % by weight of silica mixed in the polymer, and the silica was surface-treated with α,ω-bis(dimethyl hydroxysilyl) poly(dimethyl siloxane) (M = 520 g/mol), which was present in an amount of 12 % by weight in the blend.

The amounts of ingredients in the composition example were as follows:

- PEO(-PDMS-PEO)$_n$ 32.8 % by weight
- DMS-VMS copolymer containing a silica filler, 60.9 % by weight
- Platinum catalyst 0.1 % by weight
- Crosslinking agent 6.19 % by weight
- Inhibitor 0.03 % by weight

First the basic polymer blend was prepared in a chamber mixer. 4.2 grams of the PEO(-PDMS-PEO)$_n$ block copolymer and

7.8 grams of the DMS-VMS copolymer containing a silica filler were weighed into the mixing chamber. The ingredients were agitated until the blend was homogeneous.

Portion I was prepared as in Example 1.

The combining of the crosslinking agent and the inhibitor was done, as in Example 1, before mixing with portion II, except that ETCH was weighed in an amount of 0.048 g and Silopren U Vernetzer 730 in an amount of 9.952 g. The amount of inhibitor in the blend was 0.48 % by weight.

Portion II was prepared as in Example 1, except that the basic polymer blend was weighed in an amount of 4.816 grams and the mixture of the crosslinking agent and the inhibitor in an amount of 0.684 grams.

Portions I and II were combined as in Example 1. Four batches of 2.1 g of the blend were weighed and were crosslinked successively in a hot-press, as in Example 1.

EXAMPLE 3

Elastomer membrane prepared from composition type C

Ingredients used for the preparation of the elastomer membrane:

- The PEO(-PDMS-PEO)$_n$ was the same as in Example 2. The catalyst and the inhibitor were the same as in Examples 1 and 2.

- The dimethyl siloxane-vinyl methyl siloxane (DMS-VMS) copolymer containing a silica filler was the same as in Example 2.

- The crosslinking agent used was a PDMS-(-PEO-PDMS)$_n$ copolymer having a Si-H content of 0.26 mmol/g, and the

amount of PEO in it was 23.6 % by weight.

The said crosslinking agent was prepared as follows:

40 g of an anhydrous α,ω-divinyl ether poly(ethylene oxide) (PEODIVI) having a molar mass of 246.3 g/mol was weighed into a three-necked flask. In addition, 129.4 g of α,ω-bis(dimethyl silyl hydride) poly(dimethyl siloxane) (PDMSDIH, M_n = 717 g/mol) and 30 % by weight of toluene dried by distillation were weighed into the same vessel. Since dimethyl silyl hydride groups were present in excess (10 %) in the reaction, dimethyl silyl hydride groups were obtained at both ends in the final product. The reaction solution was stirred over a magnetic stirring plate at 200 rpm, and dry oxygen was directed through the solution to prevent the deactivation of the catalyst. The reaction solution was heated to 50 °C, whereafter the catalyst (Pt(0) divinyl-tetramethyl siloxane complex) was added to the solution through the septum. The amount of platinum was 30 ppm, calculated from the amount of the reactants. Thereafter the polymerization was monitored by means of IR until the reactions were complete (loss of the vinyl peak at 1600 cm^1), which took approximately 4 h. After the polymerization, the toluene was removed from the solution by distillation by raising the temperature to 65 °C and by lowering the pressure to 5 mbar for a period of 1 h.

The amounts of the ingredients in the composition example were as follows:

- $PEO(-PDMS-PEO)_n$ 1.10 % by weight
- DMS-VMS containing a silica filler, 85.50 % by weight
- Platinum catalyst 0.10 % by weight
- Crosslinking agent α,ω-bis-(dimethyl silyl hydride) PEO-PDMS 13.27 % by weight
- Inhibitor 0.03 % by weight

First the basic polymer blend was prepared in a chamber mixer. 0.15 grams of the α,ω-divinyl ether PEO-PDMS block

copolymer and 11.85 grams of the DMS-VMS copolymer containing a silica filler were weighed into the mixing chamber. The ingredients were agitated until the blend was homogeneous.

Portion I was prepared as in Example 1. The combining of the crosslinking agent and the inhibitor was done, as in Example 1, before mixing with portion II, except that ETCH was weighed in an amount of 0.022 g and PDMS-(PEO-PDMS)$_n$ block copolymer in an amount of 9.978 g instead of Vernetzer 730. The amount of inhibitor in the blend was 0.22 % by weight.

Portion II was prepared as in Example 1, except that the basic polymer blend was weighed in an amount of 4.04 grams and the mixture of the crosslinking agent and the inhibitor in an amount of 1.46 grams.

Portions I and II were combined as in Example 1. Four batches of 2.1 g of the blend were weighed and were successively crosslinked in a hot-press, as in Example 1.

EXAMPLE 4

Elastomer membrane prepared from composition type D

Ingredients used for the preparation of the elastomer membrane:

- α,ω-divinyl ether poly(ethylene oxide) (PEODIVI) (poly-ethylene glycol divinyl ether, Aldrich, M_n = 240 g/mol). The vinyl amount obtained by titration was 7.4 mmol/g.

- Catalyst Gelest SIP 6831.0, platinum-siloxane complex in xylene, platinum content 2.25 % by weight.

- The crosslinking agent and the inhibitor were the same as in Example 1.

The amounts of the ingredients in the composition example were as follows:

- PEODIVI 52.231 % by weight
- Platinum catalyst 0.045 % by weight
- Crosslinking agent 47.694 % by weight
- Inhibitor 0.030 % by weight

First a mixture of the crosslinking agent and the inhibitor was prepared as in Example 1, except that the inhibitor was weighed in an amount of 0.0063 grams and the crosslinking agent in an amount of 9.9937 grams. The amount of inhibitor in the mixture was 0.063 % by weight.

5.2231 grams of PEODIVI and 0.0045 grams of the platinum catalyst were mixed together in a glass vessel. 4.772 grams of the mixture of the crosslinking agent and the inhibitor was mixed into it.

Eight batches of 0.8 g of the blend were weighed into flat-bottomed aluminum forms having a diameter of 5 cm and having a FEP membrane on the bottom. The forms were placed under a 100 mbar vacuum at +115 °C for a period of 15 minutes. Test pieces were cut out from the elastomer obtained.

EXAMPLE 5

Elastomer membrane prepared from composition type E

Ingredients used for the preparation of the elastomer membrane:

- PEODIVI, the same as in Example 4.
- DMS-VMS copolymer, the same as in Example 2.

The catalyst, the crosslinking agent and the inhibitor were the same as in Example 1.

The amounts of the ingredients in the composition example were as follows:

- PEODIVI 11.37 % by weight
- DMS-VMS copolymer 64.46 % by weight
- Platinum catalyst 0.1 % by weight
- Crosslinking agent 24.03 % by weight
- Inhibitor 0.03 % by weight

First, a mixture of the crosslinking agent and the inhibitor was prepared, as in Example 1, except that the inhibitor was weighed in an amount of 0.0125 grams and the crosslinking agent in an amount of 9.9875 grams. The amount of inhibitor in the mixture was 0.125 % by weight.

1.138 grams of PEODIVI and 6.446 grams of DMS-VMS copolymer were mixed together in a chamber mixer. 0.01 grams of platinum catalyst was added, and the blend was agitated until homogeneous. 2.406 grams of the mixture of the crosslinking agent and the inhibitor was added and the blend was agitated until homogeneous.

Four batches of 2.1 g of the blend were weighed and were successively crosslinked in a hot-press, as in Example 1.

EXAMPLE 6

Elastomer membrane prepared from composition type F

Ingredients used for the preparation of the elastomer membrane:

- PDMS-PEO graft copolymer having a vinyl concentration of 0.0743 mmol/g and a PEO content of 1.28 % by weight.

- The catalyst, the crosslinking agent and the inhibitor were the same as in composition A.

The PDMS-PEO graft copolymer used was prepared as follows:

600 g of octamethyl cyclotetrasiloxane (D_4), 9.28 g of poly-(dimethyl siloxane)-poly(ethylene oxide) graft copolymer (Gelest, DBE-821, containing 80 % by weight PEO), 6.18 g of dimethyl vinyl silyl end-blocked PDMS (end-blocker, Bayer Silopren U2), and 3.1 g of tetramethyl tetravinyl cyclotetrasiloxane were weighed. The reactor was nitrogenated, the weighed chemicals were poured in, and stirring was started. The inside temperature of the reactor was raised to 135 °C, and the catalyst (potassium siloxanolate, 0.9 ml, 20 ppm K^+) was added to the reaction solution. The viscosity of the reaction solution began to increase vigorously, and at 1 h from the adding of the catalyst it was possible to deactivate the catalyst by increasing the reactor pressure to 2 bar for a period of 15 minutes by means of carbon dioxide. Thereafter the light cyclic compounds (13 % by weight) were removed from the reaction solution by distillation (10 mbar, 30 min, 135 °C). Product M_n = 190,000 g/mol.

The amounts of the ingredients in the composition example were as follows:

- Basic polymer PDMS-PEO graft copolymer 96.10 % by weight
- Platinum catalyst 0.5 % by weight
- Crosslinking agent 3.06 % by weight
- Inhibitor 0.34 % by weight

The combining of the crosslinking agent and the inhibitor was done as in Example 1, except that ETCH was weighed in an amount of 1.0 g and Silopren U Vernetzer 730 in an amount of 9.0 g. The amount of inhibitor in the mixture was 10 % by weight.

9.61 grams of the PDMS-PEO graft copolymer and 0.05 grams of the platinum catalyst were mixed together. 0.34 grams of the mixture of the crosslinking agent and the inhibitor was

added and the blend was stirred until homogeneous.

Four batches of 2.1 g of the blend were weighed and were successively crosslinked in a hot-press, as in Example 1.

EXAMPLE 7

Elastomer membrane prepared from composition type G

Ingredients used for the preparation of the elastomer membrane:

- The PDMS-PEO graft copolymer was the same as in Example 6.
- The DMS-VMS copolymer was the same as in Example 2.
- The catalyst, the crosslinking agent and the inhibitor were the same as in Example 1.

The amounts of the ingredients in the composition example were as follows:

- PDMS-PEO graft copolymer 26.75 % by weight
- DMS-VMS copolymer 72.31 % by weight
- Platinum catalyst 0.10 % by weight
- Crosslinking agent 0.81 % by weight
- Inhibitor 0.03 % by weight

The combining of the crosslinking agent and the inhibitor was done as in Example 1, except that ETCH was weighed in an amount of 0.36 g and Silopren U Vernetzer 730 in an amount of 9.64 g. The amount of inhibitor in the mixture was 3.6 % by weight.

2.675 grams of the PDMS-PEO graft copolymer and 7.231 grams of the DMS-VMS copolymer containing a filler were mixed together. 0.01 grams of the platinum catalyst was added and the blend was stirred until homogeneous. 0.084 grams of the mixture of the crosslinking agent and the inhibitor was

added and the blend was stirred until homogeneous.

Four batches of 2.1 g of the blend were weighed and were successively crosslinked in a hot-press, as in Example 1.

EXAMPLE 8

Elastomer membrane prepared from composition type H

Ingredients used for the preparation of the elastomer membrane:

- APEO-(-PDMS-APEO)$_n$, where the amount of PEO was 10.3 % by weight and the vinyl content 0.063 mmol/g.
- The catalyst was the same as in Example 4.
- The inhibitor was the same as in Example 1.

- The crosslinking agent was a DMS-HMS copolymer which contained 22.5 % by weight methyl hydride siloxane groups (Gelest).

The APEO-(-PDMS-APEO)$_n$ used was prepared as follows:

Anhydrous α,ω-diallyl poly(ethylene oxide) (PEODIAL) which had a molar mass of 520 g/mol and which was prepared by adapting the procedure disclosed in the publication Mei-Hui, Yang, Laing-Jong, Li, and Tsang-Feng, Ho, Synthesis and Characterization of polymethylsiloxane/poly(ethylene glycol)monomethyl ether copolymers, J. Ch. Colloid & Interface Soc. 3(17), 1994, 19-28 and α,ω-bis(dimethyl silyl hydride) poly(dimethyl siloxane) (PDMSDIH, M_n = 6000 g/mol) were weighed into a three-necked flask. The mass of the PEODIAL was 1.38 g (M_n = 520 g/mol, 5.28 mmol of allyl groups) and the mass of PDMSDIH was 12 g (4.8 mmol of hydride groups), the amount of allyl groups being 10 % greater than that of hydride groups. Thus an α,ω-diallyl-end-blocked final product was ensured.

In addition, toluene was weighed into the reaction vessel in an amount of 45 % by weight (7.2 g). The reaction mixture was stirred over a magnetic stirring plate at 200 rpm, and dry oxygen was bubbled through the mixture in order to prevent the deactivation of the catalyst. The temperature of the reaction mixture was raised to 60 °C. Thereafter the catalyst (Pt(0) divinyl tetramethyl disiloxane complex) was added to the reaction solution through the septum, cautiously one drop at the time. The amount of platinum was 50 ppm, calculated from the reactants. The polymerization was allowed to proceed for approximately 6 h, whereafter the completion of the polymerization was confirmed by IR (loss of the Si-H peak at 2130 cm^{-1}). For the removal of the toluene by distillation, the temperature was raised to 65 °C and the pressure was lowered to 5 mbar for a period of 30 min.

The amounts of the ingredients of the composition example were as follows:

- APEO-(-PMDS-APEO)$_n$ 94.68 % by weight
- Platinum catalyst 0.5 % by weight
- Crosslinking agent 4.7 % by weight
- Inhibitor 0.12 % by weight

3.0 grams of the APEO-(-PMDS-APEO)$_n$, 0.0158 grams of the catalyst, 0.0038 g of the inhibitor, and 0.1489 g of the crosslinking agent were mixed together. The air bubbles were removed from the mixture, and the mixture was crosslinked in a hot-press at 110 °C for 15 minutes and was cured at 110 °C for 15 minutes.

EXAMPLE 9

Elastomer membrane prepared from composition type I

Ingredients used for the elastomer membrane:
- PEO-(PDMS-PEO)$_n$, where the amount of PEO was 5.0 % by

weight and the vinyl content was 0.04 mmol/g.
- The DMS-VMS copolymer containing a silica filler was the same as in Example 2.
- Dichlorobenzoyl peroxide (Perkadox PD50 S, Nusil).

The PEO-(PDMS-PEO)$_n$ used was prepared as follows:

0.528 g of anhydrous α,ω-divinyl ether poly(ethylene oxide) (PEODIVI) having a molar mass of 240 g/mol was weighed into a three-necked flask. 10 g of α,ω-bis(dimethyl silyl hydride)poly(dimethyl silyl siloxane) (PDMSDIH) having a molar mass of 6000 g/mol was weighed into the same vessel. The PDMSDIH contained hydride groups in an amount of 0.04 % by weight, and thus the amount of hydride groups in 10 grams was 4 mmol and the amount of PEODIVI vinyl groups was 4.4 mmol. Since the vinyl groups were present in excess (10 %) in the reaction, vinyl groups were obtained at both ends of the final product, a fact essential for the subsequent crosslinking. In addition, to facilitate mixing and to prevent the reaction from occurring too vigorously, toluene dried by distillation was added to the reaction mixture so that the proportion of toluene was 30 % by weight (4.5 g). The reaction solution was stirred over a magnetic stirring plate at 200 rpm, and dry oxygen was directed through the solution; this prevented the catalyst from converting to metallic form and thus prevented the deactivation of the catalyst. The reaction solution was heated to 50 °C, whereafter the catalyst (Pt(0) divinyl tetramethyl disiloxane complex) was added to the mixture through the septum. The amount of platinum was 50 ppm, calculated from the amount of the reactants. The catalyst was added dropwise, whereby hot spots in the reactor were avoided. After the adding of the catalyst the reaction was allowed to proceed for 2 h. Thereafter the completion of the reaction was confirmed by IR (loss of the Si-H peak at 2130 cm^{-1}). After the polymerization the reaction mixture was heated to 65 °C and the toluene was removed by vacuum distillation (5 mbar) in the course of 30 minutes.

The amounts of ingredients in the composition example were as follows:

- PEO-(PDMS-PEO)$_n$, 4.9 % by weight
- silica-filled DMS-VMS copolymer, 93.9 % by weight
- dichlorobenzoyl peroxide (Perkadox PD50 S, Nusil), 1.2 % by weight.

0.5 g of PEO-(PDMS-PEO)$_n$ and 9.5 g of a DMS-VMS copolymer containing a filler were mixed together. 0.12 g of the peroxide catalyst was mixed with the homogeneous blend, and the blend was hardened at a temperature of +115 °C and a pressure of 200 bar for 5 minutes and was cured at +150 °C for 2 hours.

EXAMPLE 10

Elastomer membrane prepared from composition type J

Ingredients used for the preparation of the elastomer:

- PDMS-PEO graft copolymer the same as in Example 6
- Dichlorobenzoyl peroxide Perkadox PD50 S, Nusil

The amounts of the ingredients in the composition example were as follows:

- PDMS-PEO graft copolymer 98.8 % by weight
- Dichlorobenzoyl peroxide Perkadox PD50 S 1.2 % by weight

10 grams of the PDMS-PEO graft copolymer and 0.12 grams of Perkadox PD50 S were mixed together. The blend was hardened at a temperature of +115 °C and a pressure of 200 bar for 5 minutes and was cured at +150 °C for 2 hours.

Permeation tests

Various compositions, in which the amount of PEO groups

varied, were prepared of the above-mentioned composition types A - J. Composition types A - G were tested for the permeation rates of various drugs.

The assay apparatus described in the publication Yie W. Chien, Transdermal Controlled Systemic Medications, Marcel Dekker Inc., New York and Basel 1987, page 173, was used in the tests.

The drug fluxes (permeations) through membranes were measured with a two-compartment diffusion cell at 37 °C (side-by-side diffusion cell, Crown Glass Company). The apparatus consisted of two concentric cells (donor and receptor compartments) that were separated by the elastomer membrane to be investigated. The donor and receptor compartments were both jacketed and thermostated by an external circulating bath and each compartment had a magnetic stirrer. A drug solution and solvent (without drug) was added into the donor and the receptor compartments. At each predetermined time interval, samples were withdrawn from the receptor compartment and replaced with the same volume of solvent. The amount of the drug that permeated through the membrane was measured by HPLC. In all measurements, the thickness (0.4 mm) of the membrane and the surface area of the membranes were constant.

In the tests described below, the permeation rates of two different drugs through a 0.4-mm-thick elastomer membrane were measured by using the assay apparatus described above. The tables below show the effect of the concentration of PEO groups (% by weight of the said compositions) on the permeation rates of the different drugs for elastomers prepared from different composition types. The tables show the relative permeation as compared with a commercial crosslinked dimethyl siloxane-vinyl methyl siloxane elastomer (M_n approximately 400,000 g/mol) containing a silica filler.

Drug 1: Levonorgestrel

Composition type	PEO concentration % by weight	Relative permeation
comparison	0	1
A	28.0	14.5
B	3.8	1.5
B	4.1	2.0
B	5.0	2.3

Drug 2: 17-β-Estradiol

Composition type	PEO concentration % by weight	Relative permeation
comparison	0	1
A	11.6	21.3
A	26.4	110
B	7.8	13.3
B	9.8	24.4
C	3.4	4.6
D	52.3	90.4
E	11.4	7.7
F	1.3	2.4
G	0.5	1.4

The permeation tests performed showed that an increasing concentration of PEO in the membrane increased the permeation rate for each composition type and for each drug tested, regardless of whether the drug concerned was hydrophilic or lipophilic.

An elastomer composition according to the invention is, for example, highly suited for controlling, in implants and in intrauterine and intravaginal devices, the permeation rates of drugs having hormonal action.

The most important drugs having hormonal action include antiprogestins, progestins, estradiols and androgens.

The above embodiments of the invention are only examples of the implementation of the idea of the invention. For a person skilled in the art it is clear that the different embodiments of the invention may vary within the framework of the claims presented below.

CLAIMS

1. A membrane or matrix for controlling the permeation rate of a drug, said membrane or matrix comprising a siloxane-based elastomer composition comprising at least one elastomer and possibly a non-crosslinked polymer, characterized in that the elastomer composition comprises poly(alkylene oxide) groups, and that the poly(alkylene oxide) groups are present in the elastomer or polymer as alkoxy-terminated grafts of polysiloxane units, or as blocks, the said grafts or blocks being linked to the polysiloxane units by silicon-carbon bonds, or as a mixture of these forms.

2. The membrane or matrix according to Claim 1, characterized in that the elastomer composition is an elastomer made up of polysiloxane units which comprise poly(alkylene oxide) groups.

3. The membrane or matrix according to Claim 1 or 2, characterized in that the poly(alkylene oxide) groups are poly(ethylene oxide) groups (PEO groups).

4. The membrane or matrix according to Claim 2 or 3, characterized in that the formula of the polysiloxane groups is

$-(SiR'R''O)_qSiR'R''-$

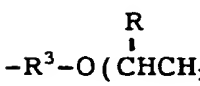
where R' and R'' are
- partly free groups, which are the same or different and which are a lower alkyl group, or a phenyl group, in which case the said alkyl or phenyl group may be substituted or unsubstituted, or alkoxy-terminated poly(alkylene oxide) groups having the formula

$-R^3-O-(\underset{\displaystyle R}{\underset{|}{CH}}-CH_2-O)_m-alk$, where alk is a lower alkyl group,

suitably methyl, R is hydrogen or a lower alkyl, R^3 is a straight-chain or branched C_2 - C_6 alkyl, and m is 1...30,
- partly bonds formed from the hydrogen or alkylene groups to other polymer chains in the elastomer, and
- possibly partly unreacted groups, such as hydrogen, vinyl or vinyl-terminated alkene, and
- q is 1...3000.

5. The membrane or matrix according to Claim 4, characterized in that the free R' and R'' groups are a lower alkyl group, preferably methyl.

6. The membrane or matrix according to Claim 2 or 3, characterized in that the poly(alkylene oxide) groups are present in the elastomer in the form of poly(alkylene oxide) blocks having the formula



or

where R is hydrogen, a lower alkyl or phenyl, R_1 is hydrogen or a lower alkyl, R^3 and R^4 are the same or different and are straight-chain or branched C_2 - C_6 alkyl groups, and m is 1...30.

7. The membrane or matrix according to Claim 1, characterized in that the elastomer composition is made up of two elastomers interlaced one inside the other, in which case
- the first elastomer comprises poly(alkylene oxide) groups, and that the poly(alkylene oxide) groups are present in the said elastomer as alkoxy-terminated grafts of polysiloxane units, or as blocks, in which case the said grafts or blocks are linked to the polysiloxane units by silicon-carbon bonds, or as a mixture of these forms, and

that
- the second elastomer is a siloxane-based elastomer.

8. The membrane or matrix according to Claim 7, characterized in that the second elastomer is a poly(dimethyl siloxane)-based elastomer which possibly comprises poly(alkylene oxide) groups.

9. The membrane or matrix according to Claim 8, characterized in that the possible poly(alkylene oxide) groups of the second poly(dimethyl siloxane)-based elastomer are present in the form of alkoxy-terminated grafts of poly(dimethyl siloxane) units, or as blocks, the said grafts or blocks being linked to the poly(dimethyl siloxane) units by silicon-carbon bonds, or as a mixture of these forms.

10. The membrane or matrix according to Claim 1, characterized in that the elastomer composition is a blend which comprises
- a siloxane-based elastomer and
- a straight-chain polysiloxane copolymer which comprises poly(alkylene oxide) groups, in which case the poly(alkylene oxide) groups are present in the said polymer as alkoxy-terminated grafts of polysiloxane units, or as blocks, the said grafts or blocks being linked to the polysiloxane units by silicon-carbon bonds, or a mixture of these forms.

11. The membrane or matrix according to Claim 10, characterized in that the poly(alkylene oxide) groups are poly(ethylene oxide) groups (PEO groups).

12. The membrane or matrix according to Claim 10 or 11, characterized in that the formula of the polysiloxane groups is

$-(SiR'R''O)_qSiR'R''-$

where R' and R'' are the same or different and are a lower alkyl group, or a phenyl group, in which case the said alkyl or phenyl group may be substituted or unsubstituted, or alkoxy-terminated poly(alkylene oxide) groups having the formula

$-R^3-O-(\overset{R}{\overset{|}{C}}H-CH_2-O)_m-alk$, where alk is a lower alkyl group, suitably methyl, R is hydrogen or a lower alkyl, R^3 is a straight or branched C_2 - C_6 alkyl group, m is 1...30, and q is 1...3000.

13. The membrane or matrix according to Claim 12, characterized in that the free R' and R'' groups are lower alkyl groups, preferably methyl.

14. The membrane or matrix according to Claim 10 or 11, characterized in that the poly(alkylene oxide) groups are present in the straight-chain polysiloxane polymer in the form of poly(alkylene oxide) blocks having the formula

$-R^3O(\overset{R}{\overset{|}{C}}HCH_2O)_mR^4-$, or

$-CH_2\overset{R_1}{\overset{|}{C}}HCOO(\overset{R}{\overset{|}{C}}HCH_2O)_mCO\overset{R_1}{\overset{|}{C}}HCH_2-$

where R is hydrogen, a lower alkyl or phenyl, R_1 is hydrogen or a lower alkyl, R^3 and R^4 are the same or different and are straight-chain or branched C_2 - C_6 alkyl groups, and m is 1...30.

15. The membrane or matrix according to Claim 10, characterized in that the siloxane-based elastomer is made up of poly(dimethyl siloxane).

16. The membrane or matrix according to any of Claims 10 - 15, characterized in that the siloxane-based elastomer

comprises poly(alkylene oxide) groups, and that the poly(alkylene oxide) groups are present in the elastomer or polymer as alkoxy-terminated grafts of polysiloxane units, or as blocks, the said grafts or blocks being linked to the polysiloxane units by silicon-carbon bonds, or as a mixture of these forms.

17. The membrane or matrix according to any of Claims 1 - 16, characterized in that it contains a filler, suitably silica.

18. A method for the preparation of a siloxane-based elastomer which comprises poly(alkylene oxide) groups and is intended for use in a membrane or matrix controlling the permeation rate of drugs, characterized in that

a) a vinyl-functional polymer component and a hydride-functional component are crosslinked in the presence of a catalyst, or
b) a polymer component is crosslinked in the presence of a peroxide catalyst.

19. The method according to Claim 18, characterized in that the amounts of the vinyl-functional component and the hydride-functional component are selected so that the ratio of the molar amount of hydrides to the molar amount of double bonds is at minimum 1.

20. The method according to Claim 18 or 19, characterized in that
I) the vinyl-functional polymer component is

a) a vinyl-functional polysiloxane having the formula

R'-Sir'R''O(SiR'R''O)$_r$SiR'R''R'

where R' and R'' are the same or different and are a lower alkyl group or a phenyl group, in which case the

said alkyl or phenyl group may be substituted or unsubstituted, and where some of the substituents R' and/or R'' have been substituted for by vinyl groups, and r is 1...27000, or

b) an alkenyl terminated polysiloxane-based block copolymer having the formula

$T(AB)_xAT$ (I), where

A = $-(SiR'R''O)_qSiR'R''-$, where R' and R'' are the same or different and are a lower alkyl group or a phenyl group, in which case the said alkyl or phenyl group may be substituted or unsubstituted;

B is a poly(alkylene oxide) having the formula

$$-R^3O(\overset{R}{\overset{|}{C}}HCH_2O)_mR^4-, \text{ or}$$

$$-CH_2\overset{R_1}{\overset{|}{C}}HCOO(\overset{R}{\overset{|}{C}}HCH_2O)_mCO\overset{R_1}{\overset{|}{C}}HCH_2- \quad \text{and T is}$$

$$R^1O(\overset{R}{\overset{|}{C}}HCH_2O)_mR^3, \text{ or}$$

$$CH_2{=}\overset{R_1}{\overset{|}{C}}COO(\overset{R}{\overset{|}{C}}HCH_2O)_mCO\overset{R_1}{\overset{|}{C}}HCH_2-$$

where R is hydrogen, a lower alkyl or phenyl, R_1 is hydrogen or a lower alkyl, R^3 and R^4 are the same or different and are straight-chain or branched C_2 - C_6 alkylene groups, R^1 is a straight-chain or branched C_2 - C_6 alkenyl group, m is 1...30, q is 1...3000, and x is 0...100, or

c) a vinyl-functional polysiloxane copolymer having the

formula

$$R'-SiR'R''O(SiR'R''O)_r(SiR'R''O)_pSiR'R''-R'$$

- where, in the first block, R' and R'' are the same or different and are a lower alkyl group, or a phenyl group, in which case the said alkyl or phenyl group may be substituted or unsubstituted, and where some of the substituents R' and/or R'' have been substituted for by vinyl groups, and r is 1...27000, and

- where, in the second block, R' is a lower alkyl group, or an alkoxy-terminated poly(alkylene oxide) group having the formula

$$-R^3-O-(\underset{R}{CH}-CH_2-O)_m-alk,$$

where alk is a lower alkyl group, suitably methyl, R^3 is a straight or branched C_2 - C_6 alkyl group, R is hydrogen or a lower alkyl group, and m is 1...30, or R' is a phenyl group, in which case the said alkyl or phenyl group may be substituted or unsubstituted, and R'' is a lower alkyl group or a phenyl group, in which case the said alkyl or phenyl group may be substituted or unsubstituted, and p is 1...5000, or

d) α,ω-dialkenyl poly(alkylene oxide) having the formula

$$R^1-O-(\underset{R}{CH_2CH_2O})_m-R^2$$

where R is hydrogen or a lower alkyl, R^1 and R^2 are the same or different straight-chain or branched C_2 - C_6 alkenyl groups, and m is 1...30, or

e) a blend of at least two of the above-mentioned components a) - d), and that

II) the hydride-functional component is

a) a hydride-functional siloxane which may be straight-chain, star shaped, branched or cyclic, or

b) a hydride-terminated siloxane-based block copolymer having the formula

$T(BA)_xBT$ (II), where

T = $H\text{-}SiR'R''O(SiR'R''O)_qSiR'R''\text{-}$,
A = $\text{-}SiR'R''O(SiR'R''O)_qSiR'R''\text{-}$, where R' and R'' are the same or different and are a lower alkyl group or a phenyl group, in which case the said alkyl or phenyl group may be substituted or unsubstituted;

B is a poly(alkylene oxide) having the formula

$$\text{-}R^3\text{-}O(\overset{R}{\overset{|}{C}}HCH_2O)_mR^4\text{-},$$ or

$$\text{-}CH_2\overset{R_1}{\overset{/}{C}}HCOO(\overset{R}{\overset{|}{C}}HCH_2O)_mCO\overset{R_1}{\overset{/}{C}}HCH_2\text{-}$$

where R is hydrogen, a lower alkyl or phenyl, R_1 is hydrogen or a lower alkyl, R^3 and R^4 are the same or different and are straight-chain or branched C_2 - C_6 alkyl groups, m is 1...30, q is 1...3000, and x is 0...100, or

c) a blend of the above-mentioned components a) and b).

21. The method according to Claim 20, characterized in that the hydride-functional siloxane copolymer is straight-chain, and that its formula is

$R'\text{-}SiR'R''O(SiR'R''O)_rSiR'R''R'$

where R′ and R′′ are the same or different and are a lower alkyl group or a phenyl group, in which case the said alkyl or phenyl group may be substituted or unsubstituted, and where some of the substituents R′ and/or R′′ have been substituted for by hydrogen, and r is 1...27000.

22. The method according to any of Claims 18 - 21, characterized in that the vinyl-functional polymer component contains a filler, suitably silica.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 99/00511

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C08L 83/12, C08G 77/46, A61K 9/58
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C08L, C08G, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, File CA, Chemical Abstracts, volume 126, no. 15, 14 April 1997 (Columbus, Ohio, US), Hu, Yunhua et al: "Synthesis and drug release property of polysiloxane containing pendant long alkyl ether group"; & Gaofenzi Xuebao (1997), (1), 62-67	1-22
X	Journal of Controlled Release, Volume 10, 1989, Katherine L. Ulman et al, "Drug permeability of modified silicone polymers. I. silicone-organic block copolymers" page 251 - page 260	1-22
P,A	US 5889108 A (SHIZHONG ZHANG), 30 March 1999 (30.03.99), abstract, claims	1-22

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 October 1999	20 -10- 1999
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Hélène Eriksson/EÖ Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 99/00511

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0882753 A1 (DOW CORNING CORPORATION), 9 December 1998 (09.12.98), abstract, claim 1	1-22

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INTERNATIONAL SEARCH REPORT

Information on patent family members

30/08/99

International application No.
PCT/FI 99/00511

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5889108 A	30/03/99	EP 0882753 A	09/12/98
		JP 11049957 A	23/02/99
EP 0882753 A1	09/12/98	JP 11049957 A	23/02/99
		US 5889108 A	30/03/99

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ÅP2647	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/FI99/00511	International filing date *(day/month/year)* 11.06.1999	Priority date *(day/month/year)* 30.06.1998
International Patent Classification (IPC) or national classification and IPC7 C 08 L 83/12, C 08 G 77/46, A 61 K 9/58		
Applicant Leiras Oy et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.12.1999	05.10.2000
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Telex 17978 PATOREG-S Facsimile No. 08-667 72 88	Authorized officer Hélène Erikson/Els Telephone No. 08-782 25 00

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FI99/00511

I. Basis of the report

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

☒ the international application as originally filed.

☐ the description, pages _____, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____.
pages _____, filed with the letter of _____.

☐ the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. _____, filed with the letter of _____.
Nos. _____, filed with the letter of _____.

☐ the drawings, ~~sheets~~/fig _____, as originally filed,
~~sheets~~/fig _____, filed with the demand
~~sheets~~/fig _____, filed with the letter of _____.
~~sheets~~/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, ~~sheets~~/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FI99/00511

V. Resoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-22	YES
	Claims		NO
Inventive step (IS)	Claims	1-22	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-22	YES
	Claims		NO

2. Citations and explanations

The claimed invention relates to a membrane or matrix for controlling the permeation rate of a drug. Said membrane comprises a siloxane-based elastomer consisting of at least one elastomer with poly(alkylene oxide)groups and possibly a non-crosslinked polymer. Also a method for preparation of the siloxane-based elastomer is claimed.

The most relevant documents cited in the search report are the following:

D1 Chemical Abstracts, vol. 126, no. 15, 14 April 1997, Hu, Yunhua et al: "Synthesis and drug release property of polysiloxane contaioning pendant long alkyl ether group"

D2 Journal of Controlled Release, vol. 10, 1989, K.L. Ulman et al "Drug permeability of modified silicone polymers. I. silicone-organic block copolymers", page 251-250

D1 relates to a siloxane-based polymer bearing pendant long-chain alkyl ether groups, i.e. simple ether groups. The claimed invention requires poly(alkylene oxide) groups.
An addition of polymer bearing ether groups slows down the permeation rate of the drug in D1, in the claimed invention the permeation rate increases if the amount of polyalkylene groups increases.

.../...

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

D2 relates to a polysiloxane and copolysiloxanes bearing pendant long alkyl ether groups, and the drug release properties of the blended rubber film. In D2, the poly(ethylene oxide), (PEO), groups are not linked to the PDMS groups by silicon-carbon bonds, but by urea bonds. The block copolymers of D2 give different results than the elastomer composition according to the claimed invention. In D2 it is stated that the increase of PEO in block copolymer increases the permeation of hydrophilic steroids, whereas the permeation of lipophilic steroids decreases. In the claimed invention the increase of PEO groups always increases the permeation rate of the drug, regardless of the lipophilic or hydrophilic nature of the drug.

In view of the above, the cited documents only disclose the general state of the art, which is not considered to be of particular relevance. Therefore, the claimed invention according to claims 1-22 is considered to fulfil the requirements of novelty, inventive step and industrial applicability.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ÅP2647	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/FI99/00511	International filing date *(day/month/year)* 11.06.1999	Priority date *(day/month/year)* 30.06.1998
International Patent Classification (IPC) or national classification and IPC7 C 08 L 83/12, C 08 G 77/46, A 61 K 9/58		
Applicant Leiras Oy et al		

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   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
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Date of submission of the demand	Date of completion of this report
06.12.1999	05.10.2000
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 88	Telex 17978 PATOREG-S
Authorized officer Hélène Erikson/Els Telephone No. 08-782 25 00	

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FI99/00511

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☐ the description, pages _____, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____.

☐ the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. _____, filed with the letter of _____,
Nos. _____, filed with the letter of _____.

☐ the drawings, ~~sheets~~/fig _____, as originally filed,
~~sheets~~/fig _____, filed with the demand
~~sheets~~/fig _____, filed with the letter of _____,
~~sheets~~/fig _____, filed with the letter of _____.

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☐ the claims, Nos. _____
☐ the drawings, ~~sheets~~/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FI99/00511

V. Resoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-22	YES
	Claims		NO
Inventive step (IS)	Claims	1-22	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-22	YES
	Claims		NO

2. Citations and explanations

The claimed invention relates to a membrane or matrix for controlling the permeation rate of a drug. Said membrane comprises a siloxane-based elastomer consisting of at least one elastomer with poly(alkylene oxide)groups and possibly a non-crosslinked polymer. Also a method for preparation of the siloxane-based elastomer is claimed.

The most relevant documents cited in the search report are the following:

D1 Chemical Abstracts, vol. 126, no. 15, 14 April 1997, Hu, Yunhua et al: "Synthesis and drug release property of polysiloxane contaioning pendant long alkyl ether group"

D2 Journal of Controlled Release, vol. 10, 1989, K.L. Ulman et al "Drug permeability of modified silicone polymers. I. silicone-organic block copolymers", page 251-250

D1 relates to a siloxane-based polymer bearing pendant long-chain alkyl ether groups, i.e. simple ether groups. The claimed invention requires poly(alkylene oxide) groups.
An addition of polymer bearing ether groups slows down the permeation rate of the drug in D1, in the claimed invention the permeation rate increases if the amount of polyalkylene groups increases.

.../...

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

D2 relates to a polysiloxane and copolysiloxanes bearing pendant long alkyl ether groups, and the drug release properties of the blended rubber film. In D2, the poly(ethylene oxide), (PEO), groups are not linked to the PDMS groups by silicon-carbon bonds, but by urea bonds. The block copolymers of D2 give different results than the elastomer composition according to the claimed invention. In D2 it is stated that the increase of PEO in block copolymer increases the permeation of hydrophilic steroids, whereas the permeation of lipophilic steroids decreases. In the claimed invention the increase of PEO groups always increases the permeation rate of the drug, regardless of the lipophilic or hydrophilic nature of the drug.

In view of the above, the cited documents only disclose the general state of the art, which is not considered to be of particular relevance. Therefore, the claimed invention according to claims 1-22 is considered to fulfil the requirements of novelty, inventive step and industrial applicability.

PCT/FI99/00511

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 26 January 2000 (26.01.00)	
International application No. PCT/FI99/00511	**Applicant's or agent's file reference** ÅP2647
International filing date (day/month/year) 11 June 1999 (11.06.99)	**Priority date** (day/month/year) 30 June 1998 (30.06.98)
Applicant JUKARAINEN, Harri et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

06 December 1999 (06.12.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer R. E. Stoffel
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

3069526

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 99/00511

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C08L 83/12, C08G 77/46, A61K 9/58
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C08L, C08G, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, File CA, Chemical Abstracts, volume 126, no. 15, 14 April 1997 (Columbus, Ohio, US), Hu, Yunhua et al: "Synthesis and drug release property of polysiloxane containing pendant long alkyl ether group"; & Gaofenzi Xuebao (1997), (1), 62-67 --	1-22
X	Journal of Controlled Release, Volume 10, 1989, Katherine L. Ulman et al, "Drug permeability of modified silicone polymers. I. silicone-organic block copolymers" page 251 - page 260 --	1-22
P,A	US 5889108 A (SHIZHONG ZHANG), 30 March 1999 (30.03.99), abstract, claims --	1-22

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 October 1999	20 -10- 1999
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Hélène Eriksson/EÖ Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 99/00511

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0882753 A1 (DOW CORNING CORPORATION), 9 December 1998 (09.12.98), abstract, claim 1 -- --------	1-22

INTERNATIONAL SEARCH REPORT

Information on patent family members

30/08/99

International application No.
PCT/FI 99/00511

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5889108 A	30/03/99	EP 0882753 A	09/12/98
		JP 11049957 A	23/02/99
EP 0882753 A1	09/12/98	JP 11049957 A	23/02/99
		US 5889108 A	30/03/99